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GUSTO V: Combination drug treatment of acute myocardial infarction

ABSTRACT

The combination of abciximab in full doses and reteplase in half doses did not significantly reduce the rate of mortality at 30 days in patients with acute ST-segment elevation myocardial infarction (MI) when compared with reteplase in full doses in the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO V) trial. However, subgroup analysis indicates that the combined regimen reduced the complications of acute MI, representing an important alternative strategy for pharmacologic reperfusion.

KEY POINTS

The combination of abciximab and half-dose reteplase failed to produce a significant reduction in 30-day mortality, the primary end point; however, it was found to be "not inferior" to reteplase alone.

Patients receiving combination therapy had significantly fewer complications of acute MI. Reinfarction and recurrent ischemia within 7 days occurred in significantly fewer patients receiving the combination. Furthermore, the need for percutaneous coronary intervention within 6 hours of randomization was significantly reduced.

Patients over age 75 were at increased risk of intracranial hemorrhage with the combination therapy. Given the demonstrated lower risk of major bleeding complications with primary percutaneous coronary intervention and improved outcomes in this age group, mechanical reperfusion should remain the method of choice.

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ALTHOUGH THE COMBINATION of abciximab (ReoPro) in full doses and reteplase (Retavase) in half doses used in the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO V) trial¹ failed to significantly reduce mortality at 30 days in patients with acute ST-segment elevation myocardial infarction (MI) compared with reteplase in full doses, this regimen is an important strategy for pharmacologic reperfusion.

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Fibrinolytics such as reteplase are a mainstay in the treatment of acute ST-segment elevation MI,²⁻⁸ yet they have key limitations:

- Only 50% to 60% of patients achieve full angiographic reperfusion, ie, Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow, within 90 minutes of initiation^{9,10} (TABLE 1)
- In many cases fibrinolytics produce TIMI 3 flow but do not achieve microvascular, tissue-level reperfusion¹¹ and thereby contribute to suboptimal outcomes¹²⁻¹⁵
- Initial reperfusion with fibrinolytics is not absolute: reocclusion soon after successful reperfusion is common and is associated with a substantially higher mortality rate.^{14,16,17}

Newer fibrin-specific agents have been developed in an attempt to improve on these limitations. Still, the benefit of fibrinolytic therapy in patients with acute ST-segment elevation MI seems to have a "ceiling."

GUSTO V aimed to find a way to overcome the limitations of current reperfusion therapy by comparing standard fibrinolytic therapy plus heparin and aspirin with the combination of a fibrinolytic (reteplase) in half doses and a platelet aggregation inhibitor



(abciximab) in full doses, plus heparin and aspirin.

In this article we discuss the results and clinical implications of this novel approach to the treatment of acute ST-segment elevation MI.

■ REASONS FOR THE GUSTO V APPROACH TO THROMBOLYSIS

Occlusion of a coronary artery, as represented clinically by acute ST-segment elevation MI, is the culmination of three processes:

- Rupture of an atherosclerotic plaque, with the resultant adhesion of circulating platelets
- Elaboration of coagulants such as thrombin
- Generation of cross-linked fibrin.

Fibrinolytic therapy alone targets only one of the three integral components of occlusive thrombus—ie, platelets, thrombin, and fibrin.

The paradox of fibrinolysis to treat coronary thrombosis

Fibrinolytics break up cross-linked fibrin, potentially restoring flow in a blocked coronary artery. However, this also has a paradoxical effect of releasing clot-bound thrombin. This accentuates the prothrombotic milieu via platelet activation,¹⁸ the resultant generation of vasoactive amines, and activation of the coagulation cascade.¹⁹ Given this prothrombotic effect of fibrinolysis, adjunctive therapies targeting thrombin and platelets seem essential.^{19,20}

The role of platelets in coronary thrombosis

The pivotal role of platelets in acute ST-segment elevation MI was established in the International Study of Infarct Survival (ISIS 2),² in which, compared with placebo, aspirin reduced mortality following MI by 23%, a risk reduction similar to that of streptokinase alone. In addition, the combination of aspirin and streptokinase appeared to have an additive beneficial effect on mortality rates. Furthermore, aspirin has been shown to decrease the risk of reocclusion following thrombolytic therapy.²¹

Other ways to target platelets. Despite these beneficial effects, aspirin inhibits only one of many pathways of platelet activation,

TABLE 1

Reperfusion rates with selected fibrinolytic agents

AGENT	90-MINUTE TIMI* 3 FLOW (%)
Streptokinase	30–35
Anistreplase	about 40
Lanoteplase (n-PA)	26–57
Alteplase (t-PA)	54–60
Reteplase (r-PA)	about 60
Tenecteplase (TNK-tPA)	about 60

*TIMI: Thrombolysis in Myocardial Infarction study

ie, the formation of thromboxane A₂. Furthermore, many people appear to be aspirin-resistant.²² These limitations prompted the search for more potent antiplatelet therapies.

At the site of arterial injury, platelets adhere to exposed collagen, von Willebrand factor, and fibrinogen. Adherent platelets are then activated by collagen, thrombin, serotonin, adenosine diphosphate, and other factors. Activated platelets degranulate, prompting secretion of vasoactive amines, clotting factors, and chemotaxins, promoting thrombin generation and platelet accumulation: in short, promoting a cycle of thrombosis. With activation, the final common pathway of platelet aggregation, the glycoprotein IIb/IIIa receptor undergoes a conformational change and becomes receptive to ligand binding.²³ Platelet aggregation culminates in a large platelet core at the site of vascular injury, an ideal milieu for thrombus formation, as well as a mechanism of resistance to thrombolysis.

The combined thrombolytic drug regimen

Recognition of the combined role of platelets, fibrin, and thrombin in arterial thrombosis provided the basis for the combination therapy tested in the GUSTO V trial, which studied the effects of the glycoprotein IIb/IIIa inhibitor abciximab (at full doses) and the fibrinolytic reteplase (at half doses) vs full-dose reteplase on 30-day mortality rates in patients

Fibrinolysis alone cannot break through the therapeutic ceiling

TABLE 2

Complications of myocardial infarction at 7 days after randomization in the GUSTO V trial

COMPLICATION	RETEPLASE (%)	COMBINATION THERAPY* (%)	P VALUE
Any complication	31.7	28.6	<.0001
Reinfarction	3.5	2.3	<.0001
Recurrent ischemia	12.8	11.3	.004
Sustained ventricular tachycardia	2.8	2.2	.020
Ventricular fibrillation	3.5	2.7	.008
Second-degree or third-degree atrioventricular block	3.3	2.7	.018

*Half-dose reteplase and full-dose abciximab

presenting with acute ST-segment elevation MI.¹

■ GUSTO V TRIAL METHODS

GUSTO V was a randomized, multicenter, open-label trial of 16,588 patients. The primary hypothesis was that the combination treatment would be superior, or not inferior, to standard fibrinolytic therapy.

The effect of treatment was assessed using mortality at 30 days after the start of treatment as the primary end point. Secondary end points included the composite of death and disabling stroke, reinfarction, recurrent ischemia, urgent revascularization, intracranial hemorrhage, non-intracranial bleeding, and mortality at 1 year. In addition, 16 complications of acute MI were prospectively defined and recorded for all patients until day 7 or hospital discharge.

Inclusion and exclusion criteria

Patients with acute ST-segment elevation MI were recruited from 820 hospitals in 20 countries. Patients were eligible if they were 18 years old or older, experienced continuous chest discomfort for at least 30 minutes but less than 6 hours from onset to randomization, and had electrocardiographic evidence of ST-segment elevation MI or new left bundle branch block.

Patients were not enrolled if immediate

catheterization and percutaneous coronary intervention (PCI) were planned as the means of primary reperfusion. However, emergency revascularization could be performed if clinically indicated for failed pharmacologic reperfusion. Patients were also excluded if they were under age 18, had documented severe hypertension on presentation (systolic blood pressure > 180 mm Hg, diastolic > 110 mm Hg), were taking warfarin, had suffered a stroke within the previous 2 years, weighed more than 120 kg, or had thrombocytopenia (platelet count < 100,000). Written informed consent was obtained from each participant.

Randomization

Patients received either standard-dose reteplase (two 10-U boluses, 30 minutes apart) or half-dose reteplase (two 5-U boluses, 30 minutes apart) plus full-dose abciximab (0.25 mg/kg bolus, and 0.125 mg/kg/minute infusion for 12 hours). Patients in both treatment arms also received aspirin (150–325 mg daily) and heparin.

Heparin dosage was determined according to the treatment arm. For patients assigned to reteplase alone, the dosage was that used in the GUSTO III trial¹⁰: a 5,000-U bolus followed by a 1,000-U/hour infusion (for patients ≥ 80 kg), or an 800-U/hour infusion for those < 80 kg. For patients in the combined-therapy group, the heparin dosage was

The primary end point of GUSTO V was 30-day mortality

**TABLE 3****Intracranial hemorrhage in the elderly in GUSTO V**

AGE	RETEPLASE (%)	COMBINATION THERAPY* (%)	ODDS RATIO (95% CONFIDENCE INTERVAL)	P VALUE
All patients	0.6	0.6	1.05 (0.71–1.56)	.79
Under age 75	0.5	0.4	0.76 (0.46–1.24)	.27
Over age 75	1.1	2.1	1.91 (0.95–3.84)	.069

*Half-dose reteplase and full-dose abciximab

reduced and weight-adjusted (60-U/kg bolus, maximum 5,000 U, 7 U/kg/hour infusion) to reduce the bleeding risk.

Adjunctive measures

The decision whether to use additional, adjunctive drug therapies, coronary angiography, and PCI was left to individual investigators.

RESULTS**30-day mortality**

The combination of abciximab and half-dose reteplase failed to produce a significant reduction in 30-day mortality, the primary end point: 468 (5.6%) patients in the combination therapy group died vs 488 (5.9%) patients in the reteplase-alone group. No differences in death rates within 24 hours or 7 days after enrollment were observed. Combination therapy met the prespecified criteria for non-inferiority to fibrinolysis alone.

Secondary end points

Patients receiving combination therapy had significantly fewer complications of acute MI (TABLE 2). Reinfarction and recurrent ischemia within 7 days occurred in significantly fewer patients receiving the combination: 2.3% vs 3.5% had reinfarction ($P < .0001$), and 11.3% vs 12.8% had recurrent ischemia ($P = .004$). Furthermore, the need for PCI within 6 hours of randomization was significantly reduced (5.6% vs 8.6%, $P < .0001$) in the combination therapy group.

Subgroup analysis demonstrated a trend toward improved outcomes with combination therapy in most groups, a trend that was most

pronounced in patients with anterior infarction, patients under age 75, and patients presenting more than 4 hours after the onset of symptoms.

Electrical, mechanical complications.

Interestingly, patients receiving combination therapy were also significantly less likely to experience severe electrical complications of MI, including ventricular fibrillation, sustained ventricular tachycardia, or high-grade atrioventricular block. A trend towards less frequent mechanical complications of MI was also noted.

Bleeding. Intracranial hemorrhage (ICH), the most feared complication of fibrinolytic therapy, occurred at similar rates in both groups of patients (0.6%, $P = .79$). However, in elderly patients (over age 75), a trend was seen towards a greater risk of intracranial hemorrhage with combination therapy (2.1% vs 1.1%, OR 1.91, $P = .069$) (TABLE 3). Patients receiving combination therapy were twice as likely to have severe or moderate bleeding, were more likely to require blood product transfusions, and were more likely to develop severe thrombocytopenia ($P < .0001$, for all three complications) than those receiving reteplase alone (FIGURE 1). Increased bleeding associated with combination therapy was not related to invasive procedures, but was instead predominantly from gastrointestinal sources or epistaxis.

CLINICAL IMPLICATIONS OF THE GUSTO V RESULTS

Even though the combination therapy did not produce a significant reduction in 30-day mor-

Bleeding risk was higher with the combination in patients over age 75

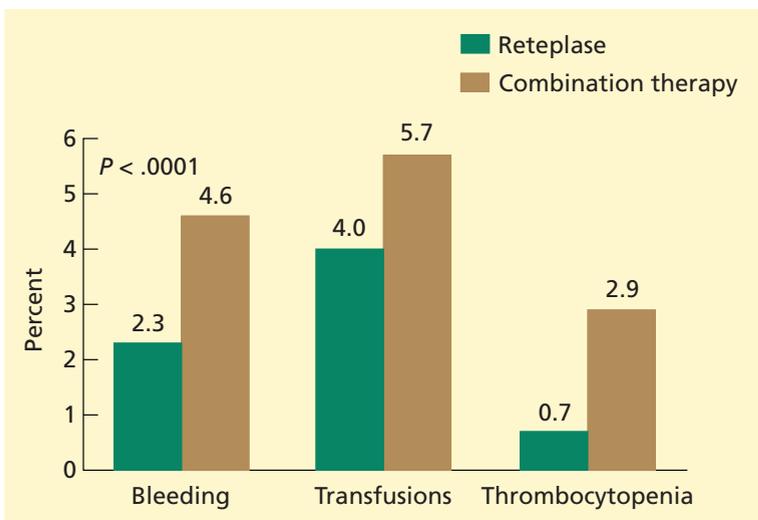


FIGURE 1. Percentage of patients with bleeding and thrombocytopenia, according to the treatment received. Bleeding is defined here as the combined rate of moderate and severe bleeding. Thrombocytopenia is defined as a platelet count < 100,000.

Lower reocclusion and reinfarction rates may translate to improved long-term survival

tality, there was evidence of more stable reperfusion with combination therapy: ie, reduced rates of reinfarction, recurrent ischemia, emergency “bailout” mechanical revascularization, and other ischemic complications. These benefits, however, were achieved at the cost of an increase in non-intracranial bleeding.

Phase 2 clinical trials had already demonstrated enhanced early patency^{24,25} and tissue-level reperfusion²⁶ with the use of a glycoprotein IIb/IIIa antagonist as an adjunct to fibrinolytic therapy in this patient population. Both of these end points have been associated with improved outcomes following acute MI.^{4,12,27} Therefore, one would expect combination therapy to be clinically beneficial.

Explaining the lack of superiority in reducing the primary end point

The lack of superiority of combination therapy in reducing 30-day mortality may be partly explained by the unusually low mortality rate of patients receiving fibrinolytic therapy alone in this trial. Clinically, this finding is encouraging, as it represents an improvement in therapy for these patients. In the GUSTO V trial, however, this low mortality rate made it

substantially more difficult to demonstrate a significant difference between the two treatment regimens.

Secondary end points

Alternatively, reocclusion and reinfarction are potentially very important end points, as their occurrence bestows an increased risk of adverse outcomes following successful reperfusion.^{16,17} Despite similar 30-day mortality rates, recurrent ischemic events represented by reocclusion and reinfarction were significantly decreased in patients receiving combination therapy. Emerging data suggest that decreases in these end point events may translate into improved long-term survival and preserved ventricular function.¹⁷ Whether the reduction in recurrent ischemic events in patients receiving combination therapy influences 1-year mortality in GUSTO V remains to be seen.

Potential indications for combined therapy

The improved freedom from recurrent ischemic events in the GUSTO V trial may not be sufficient to advocate the combined regimen for all patients with acute ST-segment elevation MI. However, certain subgroups may derive a relatively greater benefit from this therapy. Patients under age 75, patients with anterior MI, and patients presenting more than 4 hours from symptom onset demonstrated the strongest trend toward improved outcomes compared with standard fibrinolytic therapy. In fact, an absolute 0.5% to 1% decrease in mortality was seen in patients with these characteristics who received combination therapy. Nevertheless, the benefits incurred by these patients were demonstrated only in subgroup analysis and need to be further corroborated in future trials.

As an adjunct to percutaneous intervention. Although speculative at this time, combination therapy may prove beneficial in patients who are to undergo early adjunctive PCI. The use of glycoprotein IIb/IIIa inhibition as an adjunct to PCI for acute coronary syndromes has been consistently demonstrated to have substantial durable benefit and may be considered the current standard of care.^{28–30} The structure of the GUSTO V



trial, in which a planned strategy of early PCI was not permitted, did not allow evaluation of the benefit of combination therapy in patients undergoing early or primary PCI for acute infarction.

Nevertheless, there is reason to believe that a “facilitated” approach to PCI, in which combination therapy is administered prior to revascularization, could potentially combine the advantages of both strategies by taking advantage of the rapid administration of drug therapy and the proven efficacy of primary PCI. Recent trials of reduced-dose fibrinolytics and glycoprotein IIb/IIIa inhibitors have demonstrated improved tissue-level reperfusion.³¹ Moreover, facilitated PCI may prove to overcome a major limitation of primary PCI for acute ST-segment elevation MI in clinical practice—ie, delay in initiation of PCI—by achieving some degree of myocardial reperfusion during the period before the patient arrives in the catheterization laboratory. This hypothesis is being tested in two ongoing clinical trials.

The risks of combination therapy

The benefits of combination therapy are not without cost. Patients in GUSTO V who received combination therapy were significantly more likely to experience bleeding and to need blood transfusions. Although intracranial hemorrhage occurred at similar rates in both treatment groups, patients over age 75 who received the combined regimen were at higher risk. Given the increase in bleeding complications, the balance of hemorrhagic

risk vs ischemic benefit must be assessed for individual patients.

■ GUIDELINES FOR USE OF COMBINED PHARMACOLOGIC REPERFUSION IN ACUTE MI

Although the combination of abciximab and half-dose reteplase did not significantly reduce mortality at 30 days in patients with acute ST-segment elevation MI, this regimen represents an important alternative strategy for pharmacologic reperfusion. An important advantage is the apparently improved stability and completeness of reperfusion, which may be of particular benefit to patients who have larger (anterior) MIs or present later, or for whom early PCI may be anticipated. Combination drug therapy may also prove to be a useful therapeutic bridge to PCI in patients who present to institutions without a catheterization lab.

Caution is needed in patients over age 75, who are at increased risk of intracranial hemorrhage with combination therapy. Given the demonstrated lower risk of major bleeding complications with primary PCI and improved outcomes in elderly patients,³² mechanical reperfusion should remain the method of choice in these patients.

We believe the GUSTO V trial adds another dimension to the therapy of patients presenting with acute ST-segment elevation MI by targeting all three components of arterial thrombosis. With the emerging data regarding other combination chemotherapy regimens, as well as facilitated PCI, outcomes for these patients continue to be incrementally improved. 

**GUSTO V
adds another
dimension
to therapy
of acute
ST-segment MI**

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